REMARKS

The Invention

The invention is directed to methods for producing biochips comprising spotting binding agents and probes onto the biochip surface such that the probe does not bind to an area of the biochip where the binding agent is not spotted. A significant feature of one aspect of the claimed invention is that the binding agent is only provided on the portions of the biochip surface wherein the probes are to be spotted. No binding agent is provided on portions of the biochip surface where no probes are to be spotted. It is the spotting pattern of the binding agent that determines the final spotting architecture of the immobilized probe. Thus, noise or "background" produced upon detection of sample binding to probe (e.g., after hybridization of a nucleic acid sample to a immobilized oligonucleotide probe) is reduced.

Status of the Claims

Pending claims

Claims 4 to 12 and 21 to 23 are pending. In Applicants' previous response, claims 1 to 3 and 16 to 20 were canceled, claims 4 to 8 were amended and new claims 21 to 23 were added.

Restriction Requirement and Election

The claims as filed were restricted into three Groups in the Restriction Requirement dated May 3, 2000. Group I, drawn to biochips, was elected.

Claims amended, canceled and added in the instant amendment

Claims 4, 5, 8 and 22 are canceled, without prejudice, claims 6, 7, 21 and 23 are amended and new claims 24 to 36 are added. Thus, after entry of the instant amendment, claims 6, 7, 21 and 23 to 36 will be pending.

Outstanding Rejections

Applicants acknowledge that the Examiner has withdrawn all previous rejections in the Office Action of Paper No. 11, dated July 07, 2001, in view of Applicants' amendments. Thus, the outstanding rejections are new rejections.

Claims 4 to 8 and 21 to 23 stand rejected under 35 U.S.C. §112, second paragraph.

Claims 4 to 8 and 23 stand rejected under 35 USC §102(b) as allegedly anticipated by U.S. Patent No. 5,843,767, Beattie, K.L., issued December 1, 1998, filed April 10, 1996 (hereinafter "Beattie"). Claims 4 to 6, 8 and 23 stand rejected under 35 USC §102(b) as allegedly anticipated by U.S. Patent No. 6,143,499, Mirzabekov, et al., filed June 19, 1998 (hereinafter " Mirzabekov"). Claims 4 to 8 and 23 stand rejected under 35 USC §102(b) as allegedly anticipated by Bradley, WO 99/57323, published November 11, 1999.

Claim 21 stands rejected under 35 USC §103(a) as allegedly unpatentable over Beattie in view of U.S. Patent No. 6,110,426, Shalon, et al., filed December 30, 1997. Claims 22 to 23 and 6 to 7 stand rejected under 35 USC §103(a) as allegedly unpatentable over Beattie in view of U.S. Patent No. 5,601,980, Gordon, et al., issued February 11, 1997. Claim 21 stands rejected under 35 USC §103(a) as allegedly unpatentable over Mirzabekov in view of Shalon. Claims 22 to 23 and 6 stand rejected under 35 USC §103(a) as allegedly unpatentable over Mirzabekov in view of Gordon. Claim 7 stands rejected under 35 USC §103(a) as allegedly unpatentable over Mirzabekov in view of Gordon, as applied to claims 22 to 23 and 6, and further in view of Beattie. Claim 21 stands rejected under 35 USC §103(a) as allegedly unpatentable over Bradley in view of Shalon. Claims 22 to 23 and 6 to 7 stand rejected under 35 USC §103(a) as allegedly unpatentable over Bradley in view of Gordon.

Applicants respectfully traverse all outstanding objections to the specification and rejections of the claims.

The Telephonic Interview

Applicants thank the Examiner for the helpful telephonic interview on May 09, 2001, with Applicants' representative Mi K. Kim. In that interview, Applicants requested permission to cancel the previously elected claims and amend non-elected claims while filing a Request for Continued Prosecution (RCE). The Examiner gave Applicants permission to do so.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Support for new claims 24, 25 and 26 can be found, *inter alia*, on page 4, lines 2 to 14; page 5, lines 1 to 11.

Informalities

Claims Objections

Claim 7 was objected to because of an informality; the instant amendment addresses this issue.

Issues under 35 U.S.C. §112, second paragraph

Claims 4 to 8 and 21 to 23 stand rejected under 35 U.S.C. §112, second paragraph.

The phrase "spotting mixtures of respective probes and the binding agent on the plate"

Claims 4, 6 to 8, 21 and 23 are alleged to be indefinite in claim 4 for the recitation of the phrase "spotting mixtures of respective probes and the binding agent on the plate" because, as alleged by the Patent Office, "respective" is a relational term, and it is unclear what relationship if being defined. It was also alleged that the recitation was unclear as to whether one step of spotting was claimed. It was also alleged that the recitation was unclear as to whether "spotting" described the resulting appearance or the method of spotting. It was suggested that claim 4 be amended.

The instant amendment addresses this issue; claim 4 is canceled, without prejudice, and new claims 24, 25 and 26 are added.

The phrases "spotting a binding agent" and "spotting the probes"

Claims 4 to 23 are alleged to be indefinite in claims 5 and 22 for the recitation of the phrases "spotting a binding agent" and "spotting the probes" because was it unclear as to whether "spotting" described the resulting appearance or the method of spotting. It was suggested that claims 5 and 22 be amended.

The instant amendment addresses this issue; claims 4, 5 and 22 are canceled, without prejudice, and new claims 24, 25 and 26 are added.

The "spotting" step

Claims 4 to 23 are alleged to be indefinite in claims 5 and 22 because was it unclear as to whether the method comprises one step of spotting or two. It was suggested that claims 5 and 22 be amended.

The instant amendment addresses this issue; claims 5 and 22 are canceled, without prejudice, and new claims 24, 25 and 26 are added.

The phrase "where the binding agent is spotted with a spotting pin"

Claims 5, 6 to 7, 21 and 23 are alleged to be indefinite in claim 5 for the recitation of the phrase "where the binding agent is spotted with a spotting pin" because was it unclear as to whether the binding agent or the probe is "spotted" with a pin. It was suggested that claim 5 be amended.

The instant amendment addresses this issue; claim 5 is canceled, without prejudice, and new claims 24 to 27 are added.

The phrase "probes are spotted with a tube"

Claims 22, 6 to 7 and 23 are alleged to be indefinite in claim 22 for the recitation of the phrase "probes are spotted with a tube" because was it unclear as to whether the probes are "spotted" with a tube. It was suggested that claim 5 be amended.

The instant amendment addresses this issue; claim 22 is canceled, without prejudice, and new claims 24 to 29 are added.

Issues under 35 U.S.C. §102

U.S. Patent No. 5,843,767, Beattie, K.L.

Claims 4 to 8 and 23 stand rejected under 35 USC §102(b) as allegedly anticipated by U.S. Patent No. 5,843,767, Beattie, K.L., issued December 1, 1998, filed April 10, 1996.

The legal standard for anticipation under 35 U.S.C. §102 is one of strict identity. To anticipate a claim, a single prior source must contain each and every limitation of the claimed invention.

Beattie is cited for allegedly disclosing a method for producing a biochip comprising spotting mixtures of probes and the binding agent on a plate, the Patent Office noting column 6, lines 21 to 26 of Beattie.

The claimed invention is drawn to methods for producing biochips comprising a plurality of spots comprising probes, the methods including spotting a binding agent and a probe, or a mixture thereof, to a plurality of positions on the surface of the biochip; wherein the probe does not bind to an area of the biochip where the binding agent is not spotted.

Applicants respectfully aver that Beattie does not teach a method for making biochips comprising spotting a surface with binding agents for probes, such that the probe does not bind to an area of the biochip where the binding agent is not spotted. Beattie's devices comprise a multiplicity of discrete and isolated regions, such as, e.g., a series of wells (see, e.g., Figs. 1 A, 2 to 4) or orifices (see, e.g., column 10, lines 35 to 44). Beattie's device is best described as an "array of orifices," or a "polymeric array of orifices" (see, e.g., column 10, lines 36 to 46). The wells, or orifices, are first coated with a binding agent (e.g., an epoxysilane if the bottom of the indentation is glass). In Beattie, to deliver a binding agent, a "solution is flowed into the pores" of an orificed device (e.g., a glass wafer; see, e.g., column 13, lines 55 to 61). Beattie's intention is to coat the entire pore, including the walls of the pore, see, e.g., column 13, lines 46 to 49, and Example 4.

Next, a biomolecule, e.g., a nucleic acid molecule, is attached (see, e.g., column 6, lines 21 to 26). As described in Example 4 (column 13), to affix a binding agent, it is "flowed into the pores." Thus, Beattie does not describe or suggest a method that "spots" a binding agent, such that when the probe is applied, it does not bind to an area of the biochip where the binding agent is not spotted. Different biomolecules, e.g., a single DNA species are isolated into "discrete and isolated regions" because the wells physically separate the different species, not because the binding agent has been spotted. The method of Beattie could not work if the biochip surface was substantially planar, as is the case in one embodiment of the claimed invention. The method of Beattie could not work if the biochip surface was non-porous (see, e.g., Example 6, column 15), as is the case in one embodiment of the claimed invention.

The Patent Office has cited Example 4, column 13, line 51 to column 14, line 11, in support of the allegation that Beattie discloses a method that involves spotting. However, as

noted above, Beattie's method does not spot a binding agent onto a surface; Beattie's method flows a solution of binding agent through a pore.

The Patent Office has cited Example 5, column14, lines 16 to 28, in support of the allegation that Beattie discloses use of a spotting pin. However, Beattie does not describe spotting a binding agent, as in the claimed invention. The method described by Beattie uses a precision delivery system only to deliver biomolecules, e.g., DNA, oligonucleotides, not a binding agent. As noted above, in Beattie, to deliver a binding agent, a "solution is flowed into the pores" of an orificed device.

The Patent Office has also cited Example 4, column13, lines 55 to 64, in support of the allegation that Beattie discloses a plate that is substantially planar. However, Beattie does not describe a biochip with a planar surface, Beattie's devices comprise a multiplicity of orifices, such as pores or wells. Column 13, lines 55 to 61, Beattie uses a pored glass wafer over which a solution comprising a binding agent is flowed.

Accordingly, Beattie is not a single source that contains each and every limitation of the claimed invention, a method for making a biochip.

U.S. Patent No. 6,143,499, Mirzabekov, et al.

Claims 4 to 6, 8 and 23 stand rejected under 35 USC §102(b) as allegedly anticipated by U.S. Patent No. 6,143,499, Mirzabekov, et al., filed June 19, 1998 (hereinafter "Mirzabekov").

Mirzabekov is cited for allegedly disclosing a method for producing a biochip comprising spotting mixtures of probes and binding agents (i.e., a gel) on a plate, the Patent Office noting column 4, lines 50 to 61, of Mirzabekov.

The claimed invention is drawn to methods for producing biochips comprising a plurality of spots comprising probes, the methods including spotting a binding agent and a probe, or a mixture thereof, to a plurality of positions on the surface of the biochip; wherein the probe does not bind to an area of the biochip where the binding agent is not spotted.

Applicants respectfully aver that Mirzabekov does not teach a method for making biochips comprising spotting a surface with binding agents for probes, such that the probe does not bind to an area of the biochip where the binding agent is not spotted. Mirzabekov discloses a

method for making a biochip comprising spotting oligonucleotides to a gel pad mold, i.e., a binding agent. In Mirzabekov's method, the "gel pad mold," and thus, the binding agent is not spotted to a surface. As noted in noting column 4, lines 57 to 61, of Mirzabekov, "[a] detailed description of the array manufacturing procedure is contained in a co-pending U.S. patent application, having Ser. No. 08/592,120, assigned to the instant Assignee, and incorporated herein by reference." USSN 08/592,120, Mirzabekov, et al., issued as United States Patent No. 5,861,247, January 19, 1999, a copy of which is enclosed in the accompanying Information Disclosure Statement. In Mirzabekov's method, as disclosed in USSN 08/592,120, the binding agent is coated over the entire surface of the biochip. The "gel pad molds" upon which oligonucleotides are spotted are generated by light activation of a light sensitive composition in the gel pad, which coats the entire surface of the chip, as summarized by the abstract:

> The invention also provides for a method for constructing oligonucleotide matrices comprising confining light sensitive fluid to a surface, exposing said light-sensitive fluid to a light pattern so as to cause the fluid exposed to the light to coalesce into discrete units and adhere to the surface; and contacting each of the units with a set of different oligonucleotide molecules so as to allow the molecules to disperse into the units.

See also the section entitled "Array Manufacturing Detail," column 3, line 61, to column 5, line 55. Accordingly, because Mirzabekov does not teach a method for making biochips comprising spotting a surface with binding agents for probes, it is not a single source that contains each and every limitation of the claimed invention.

Bradley, et al., WO 99/57323

Claims 4 to 8 and 23 stand rejected under 35 USC §102(b) as allegedly anticipated by Bradley, et al., WO 99/57323, published November 11, 1999.

Bradley is cited for allegedly disclosing a method for producing a biochip comprising spotting mixtures of probes and binding agents (i.e., silane-modification) on a plate, the Patent Office noting page 13, lines 3 to 20, and page 15, line 24 to 33.

The claimed invention is drawn to methods for producing biochips comprising a plurality of spots comprising probes, the methods including first spotting a binding agent and then a probe, or, spotting a mixture of binding agent and probe, to a plurality of positions on the surface of a biochip.

Applicants respectfully aver that Bradley does not teach a method for making biochips comprising spotting a surface with binding agents for probes, the binding agents being spotted either before application of a probe or as a mixture with a probe. Bradley discloses a method for making a biochip comprising spotting modified oligonucleotides to a surface. The oligonucleotides are modified such that a binding agent is covalently attached. Thus, a single molecule is applied to a surface of an untreated biochip surface. In contrast, Applicants' claimed methods comprise first spotting a binding agent and then a probe, or, spotting a mixture of a binding agent and a probe.

Bradley's modified nucleic acids would not work in one embodiment of Applicants' methods - in Applicants' methods no binding agent is provided on the portions of the plate where the probes are not desired. In Applicants' methods, it is the precise application of binding agent that determines the geometry and distribution of nucleic acid immobilization on the chip surface; thus, nucleic acid placement need not be so precise. In Applicants' methods, because the probe does not bind to an area of the biochip where the binding agent is not spotted, noise produced upon detection of sample bound to immobilized oligo is reduced (i.e., signal to noise ratio is enhanced for high sensitivity).

Accordingly, because Bradley does not teach a method for making biochips comprising spotting a surface with a binding agent, either alone or as a mixture, it is not a single source that contains each and every limitation of the claimed invention.

In view of the above remarks, Applicants submit that the pending claimed invention is distinguished and not anticipated by the cited art. Accordingly, the Examiner is respectfully requested to withdraw the rejections under 35 U.S.C. §102(b).

Issues under 35 U.S.C. §103(a)

Beattie in view of U.S. Patent No. 6,110,426, Shalon, et al.

Claim 21 stands rejected under 35 USC §103(a) as allegedly unpatentable over Beattie in view of U.S. Patent No. 6,110,426, Shalon, et al., filed December 30, 1997.

Claim 21 as amended reads "The method of claim 27 [a new claim], wherein the pin comprises at least one recessed tip. Claim 27 as amended is directed to the method of claim 24, claim 25 or claim 26 [new claims], wherein the mixture, the probe or the binding agent is

spotted with a pin. New claims 24, claim 25 and claim 26, are directed to methods for producing biochips comprising first spotting a binding agent and then a probe, or, spotting a mixture of binding agent and probe, to a plurality of positions on the surface of a biochip.

As discussed above, Applicants respectfully aver that Beattie is deficient in that it does not disclose spotting a binding agent. The Patent Office has cited Example 4, column 13, line 51 to column 14, line 11, in support of the allegation that Beattie discloses a method that involves spotting. However, as noted above, Beattie's method does not spot a binding agent onto a surface; Beattie's method flows a solution of binding agent through a pore or an orifice. The method described by Beattie uses a precision delivery system only to deliver biomolecules, e.g., DNA, oligonucleotides, not a binding agent. As noted above, in Beattie, to deliver a binding agent, a "solution is flowed into the pores" of an orificed device.

Shalon does not cure this defect in Beattie. Shalon does not does not disclose spotting a binding agent.

The Patent Office also cites Shalon for allegedly producing a biochip comprising spotting probes on a plate at positions where the binding agent is located (noting column 7, lines 36 to 46, of Shalon), wherein the spotting pin comprises at least one recessed tip (noting column 7, lines 3 to 17, of Shalon).

However, Shalon does not disclose a spin with a recessed tip. The cited column 7, lines 3 to 17, of Shalon, reads;

> FIG. 1 illustrates, in a partially schematic view, a reagent-dispensing device 10 useful in practicing the method. The device generally includes a reagent dispenser 12 having an elongate open capillary channel 14 adapted to hold a quantity of the reagent solution, such as indicated at 16, as will be described below. The capillary channel is formed by a pair of spaced-apart, coextensive, elongate members 12a, 12b which are tapered toward one another and converge at a tip or tip region 18 at the lower end of the channel. More generally, the open channel is formed by at least two elongate, spaced-apart members adapted to hold a quantity of reagent solutions and having a tip region at which aqueous solution in the channel forms a meniscus, such as the concave meniscus illustrated at 20 in FIG. 2A. The advantages of the open channel construction of the dispenser are discussed below.

A recessed tip is not disclosed in this section.

In Shalon, claim 1 is directed to a method of forming a microarray of discrete analyte-assay regions on a solid support comprising use of a reagent-dispensing device having a

tip region at which the channel is open-sided and the solution in the channel forms a meniscus. The Summary in Shalon (column 3, lines 24 to 36) reads:

> The method involves first loading a solution of a selected analyte-specific reagent in a reagent-dispensing device having ... and (iii) having a tip region at which aqueous solution in the channel forms a meniscus. The channel is preferably formed by a pair of spaced-apart tapered elements.

In summary, Shalon neither discloses nor suggests spotting a binding agent or use of a recessed tip for spotting. Thus, because Shalon does not cure the defects in Beattie, a *prima facie* case of obviousness has not been made, and the rejection of claim 21 over Beattie in view of Shalon can be properly withdrawn.

Beattie in view of U.S. Patent No. 5,601,980, Gordon, et al.

Claims 22 to 23 and 6 to 7 stand rejected under 35 USC §103(a) as allegedly unpatentable over Beattie in view of U.S. Patent No. 5,601,980, Gordon, et al., issued February 11, 1997.

Claim 22 is canceled in the instant amendment. New claims 24, claim 25 and claim 26, are added; they are directed to methods for producing biochips comprising first spotting a binding agent and then a probe, or, spotting a mixture of binding agent and probe, to a plurality of positions on the surface of a biochip.

As discussed above, Applicants respectfully aver that Beattie is deficient in that it does not disclose spotting a binding agent. The Patent Office has cited Example 4, column 13, line 51 to column 14, line 11, in support of the allegation that Beattie discloses a method that involves spotting. However, as noted above, Beattie's method does not spot a binding agent onto a surface; Beattie's method flows a solution of binding agent through a pore or an orifice. The method described by Beattie uses a precision delivery system only to deliver biomolecules, e.g., DNA, oligonucleotides, not a binding agent. As noted above, in Beattie, to deliver a binding agent, a "solution is flowed into the pores" of an orificed device.

Gordon does not cure this defect in Beattie. Gordon does not does not disclose spotting a binding agent.

The Patent Office also cites Gordon for allegedly producing a biochip comprising spotting with a tube, column 4, lines 12 to 23, of Gordon. However, Gordon does not does not teach or suggest spotting a binding agent with any device, including a tube.

In summary, Gordon neither discloses nor suggests spotting a binding agent or use of a recessed tip for spotting. Thus, because Gordon does not cure the defects in Beattie, a *prima facie* case of obviousness has not been made, and the rejection of claims 22 to 23 and 6 to 7 over Beattie in view of Gordon can be properly withdrawn.

Mirzabekov in view of Shalon

Claim 21 stands rejected under 35 USC §103(a) as allegedly unpatentable over Mirzabekov in view of Shalon.

Claim 21 as amended reads "The method of claim 27 [a new claim], wherein the pin comprises at least one recessed tip. Claim 27 as amended is directed to the method of claim 24, claim 25 or claim 26 [new claims], wherein the mixture, the probe or the binding agent is spotted with a pin. New claims 24, claim 25 and claim 26, are directed to methods for producing biochips comprising first spotting a binding agent and then a probe, or, spotting a mixture of binding agent and probe, to a plurality of positions on the surface of a biochip.

As discussed above, Applicants respectfully aver that Mirzabekov is deficient in that it does not disclose spotting a binding agent. The Patent Office has cited column 11, lines 40 to 67 of Mirzabekov, to support the allegation that Mirzabekov teaches a method for producing a biochip comprising, inter alia, spotting a binding agent. However, Mirzabekov does not disclose spotting a binding agent. Mirzabekov discloses a method for making a biochip comprising spotting oligonucleotides to a gel pad mold, i.e., a binding agent. In Mirzabekov's method, the "gel pad mold," and thus, the binding agent is not spotted to a surface. In Mirzabekov's method, the binding agent is coated over the entire surface of the biochip. The "gel pad molds" upon which oligonucleotides are spotted are generated by light activation of a light sensitive composition in the gel pad, which coats the entire surface of the chip.

As discussed above, Shalon neither discloses nor suggests spotting a binding agent. Because Shalon does not cure the defects in Mirzabekov, a *prima facie* case of

obviousness has not been made, and the rejection of claim 21 over Beattie in view of Shalon can be properly withdrawn.

Mirzabekov in view of Gordon

Claims 22 to 23 and 6 stand rejected under 35 USC §103(a) as allegedly unpatentable over Mirzabekov in view of Gordon.

Claim 22 is canceled in the instant amendment. New claims 24, claim 25 and claim 26, are added; they are directed to methods for producing biochips comprising first spotting a binding agent and then a probe, or, spotting a mixture of binding agent and probe, to a plurality of positions on the surface of a biochip.

As discussed above, Applicants respectfully aver that Mirzabekov is deficient in that it does not disclose spotting a binding agent. In Mirzabekov, the binding agent, or "gel pad mold," coats the entire surface of the chip. Light is used to activate the binding agent in defined areas on the pad. Mirzabekov does not spot a binding agent onto a chip.

Gordon does not cure this defect in Mirzabekov. As discussed above, Gordon does not does not disclose spotting a binding agent.

Because Gordon does not cure the defects in Mirzabekov, a *prima facie* case of obviousness has not been made, and the rejection of claim 22 to 23 and 6 over Mirzabekov in view of Gordon can be properly withdrawn.

Mirzabekov in view of Gordon, further in view of Beattie

Claim 7 stands rejected under 35 USC §103(a) as allegedly unpatentable over Mirzabekov in view of Gordon, as applied to claims 22 to 23 and 6, and further in view of Beattie.

Claim 7, after entry of the instant amendment, is directed to the method of claim 24, claim 25 or claim 26 [new claims] wherein the binding agent is a poly-1-lysine carbodiimide or a silylation-coating. New claims 24, claim 25 and claim 26, are directed to methods for producing biochips comprising first spotting a binding agent and then a probe, or, spotting a mixture of binding agent and probe, to a plurality of positions on the surface of a biochip.

As discussed above, Mirzabekov is deficient in that it does not disclose spotting a binding agent. Gordon does not cure this defect in Mirzabekov. Gordon does not does not disclose spotting a binding agent.

Beattie also does not cure the defect in Mirzabekov. As discussed above, Beattie's method does not spot a binding agent onto a surface. In Beattie, to deliver a binding agent, a "solution is flowed into the pores" of an orificed device.

Because neither Gordon nor Beattie cure the defects in Mirzabekov, a *prima facie* case of obviousness has not been made, and the rejection of claim 7 over Mirzabekov in view of Gordon, and further in view of Beattie, can be properly withdrawn.

Bradley in view of Shalon

Claim 21 stands rejected under 35 USC §103(a) as allegedly unpatentable over Bradley in view of Shalon.

Claim 21 as amended reads "The method of claim 27 [a new claim], wherein the pin comprises at least one recessed tip. Claim 27 as amended is directed to the method of claim 24, claim 25 or claim 26 [new claims], wherein the mixture, the probe or the binding agent is spotted with a pin. New claims 24, claim 25 and claim 26, are directed to methods for producing biochips comprising first spotting a binding agent and then a probe, or, spotting a mixture of binding agent and probe, to a plurality of positions on the surface of a biochip.

As discussed above, Bradley does not teach a method for making biochips comprising spotting a surface with a binding agent, either alone or as a mixture.

Bradley discloses a method for making a biochip comprising spotting modified oligonucleotides. The binding agent is covalently attached to the oligonucleotide. Thus, a single molecule is applied to a surface of an untreated biochip surface. In contrast, Applicants' claimed methods comprise first spotting a binding agent and then a probe, or, spotting a mixture of a binding agent and a probe.

Shalon does not cure this defect in Bradley. Shalon does not does not disclose spotting a binding agent.

Also, as discussed above, Shalon neither discloses nor suggests spotting a binding agent or use of a recessed tip for spotting. Thus, because Shalon does not cure the defects in

Bradley, a *prima facie* case of obviousness has not been made, and the rejection of claim 21 over Beattie in view of Shalon can be properly withdrawn.

Bradley in view of Gordon

Claims 22 to 23 and 6 to 7 stand rejected under 35 USC §103(a) as allegedly unpatentable over Bradley in view of Gordon.

Claim 22 is canceled in the instant amendment. New claims 24, claim 25 and claim 26, are added; they are directed to methods for producing biochips comprising first spotting a binding agent and then a probe, or, spotting a mixture of binding agent and probe, to a plurality of positions on the surface of a biochip.

As discussed above, Applicants respectfully aver that Bradley is deficient in that it does not teach a method for making biochips comprising spotting a surface with a binding agent, either alone or as a mixture.

Gordon does not cure this defect in Bradley. As discussed above, Gordon does not does not disclose spotting a binding agent.

Because Gordon does not cure the defects in Bradley, a *prima facie* case of obviousness has not been made, and the rejection of claims 22 to 23 and 6 to 7 over Bradley in view of Gordon can be properly withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner should withdraw the rejection of the pending claims under 35 U.S.C. §112, second paragraph and 35 U.S.C. §102 and §103. Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If necessary, please apply additional and necessary charges, and apply all credits, to Deposit Account No. 06-1050.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Respectfully submitted,

Date: Aug 22, 2001

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Applicant : Ito et al. Art Unit : 1655
Serial No. : 09/451,666 Examiner : B.J. Forman, Ph.D.
Filed : November 30, 1999
Title : BIOCHIP AND METHOD FOR PRODUCING THE SAME

In The Specification:

The specification has been amended as follows.

On page 1, the pending title has been replaced in its entirety with the following new title:

--METHODS FOR PRODUCING BIOCHIPS--

On page 1, line 1, before the heading "FIELD OF THE INVENTION" please add the following paragraph:

-- CROSS-REFERENCES TO RELATED APPLICATIONS

The present application claims the benefit of priority under 35 U.S.C. §119 of a foreign priority patent application filed in Japan, serial number 341604/1998, filed December 1, 1998. This application is explicitly incorporated herein by reference in its entirety and for all purposes.--

In The Claims:

Claims 4, 5, 8 and 22, have been canceled, without prejudice.

Claim 6 has been amended as follows:

6. (Twice amended) The method [for producing a biochip according to] of claim 26 [4, claim 5, or claim 22], wherein the plate [is made of] comprises a material [which is] selected from the group consisting of a nylon membrane [membranes], a glass, a silicone wafer, a polyimide resin and a polymer plastic.

Claim 7 has been amended as follows:

7. (Twice amended) The method [for producing a biochip according to] of claim 24, claim 25 or claim 26 [4, claim 5, or claim 22], wherein the binding agent is

selected from the group consisting of a poly-1-lysine carbodiimide and a silylation-coating.

Claim 21 has been amended as follows:

21. (Amended) The method [for producing a biochip according to] of claim 27 [5 or claim 8], wherein the [spotting] pin comprises at least one recessed tip.

Claim 23 has been amended as follows:

23. (Amended) The method for producing a biochip according to claim 26 [5, claim 8, or claim 22], wherein the plate is substantially planar.

The following new claims have been added:

24. (NEW) A method for producing a biochip comprising a plurality of spots comprising probes, the method comprising the following steps:

(a) providing a binding agent, wherein the binding agent is capable of immobilizing a probe to the biochip, and a probe;

(b) spotting the binding agent to a plurality of positions on the biochip; and

(c) spotting a plurality of probes onto the positions spotted in step (b), wherein the binding agent is only provided on an area of the biochip where a probe is to be spotted, thereby producing a biochip comprising a plurality of spots comprising probes.

25. (NEW) A method for producing a biochip comprising a plurality of spots comprising probes, the method comprising the following steps:

(a) providing a mixture of a binding agent and a probe, wherein the binding agent is capable of immobilizing the probe to the biochip; and

(b) spotting the mixture to a plurality of positions on the biochip; wherein the binding agent is only provided on an area of the biochip where a probe is to be spotted, thereby producing a biochip comprising a plurality of spots comprising probes.

26. (NEW) A method for producing a biochip comprising a plate comprising a plurality of spots comprising probes, the method comprising the following steps:

(a) providing a plate;

(b) providing a mixture of a binding agent and a probe, wherein the binding agent is capable of immobilizing the probe to the plate; and

(c) spotting the mixture to a plurality of positions on the plate; wherein the binding agent is only provided on an area of the biochip where a probe is to be spotted, thereby producing a biochip comprising a plurality of spots comprising probes.

27. (NEW) The method of claim 24, claim 25 or claim 26, wherein the mixture, the probe or the binding agent is spotted with a pin.

28. (NEW) The method of claim 24, claim 25 or claim 26, wherein the mixture, the probe or the binding agent is spotted with a tube.

29. (NEW) The method of claim 28, wherein the tube is a capillary tube.

30. (NEW) The method of claim 27, wherein the pin comprises a tip comprising at least one recess.

31. (NEW) The method of claim 30, wherein the recess comprises concave shape.

32. (NEW) The method of claim 31, wherein the recess comprises at least one groove.

33. (NEW) The method of claim 32, wherein the groove comprises a radially-shaped groove.

34. (NEW) The method of claim 24, claim 25 or claim 26, wherein the mixture, the probe or the binding agent is suctioned by a pin and spotted on a plurality of positions on the biochip or the plate.

35. (NEW) The method of claim 24, claim 25 or claim 26, wherein the mixture, the probe or the binding agent is carried by a tip of a pin and spotted on a plurality of positions on the biochip or the plate.

36. (NEW) The method of claim 24, claim 25 or claim 26, wherein the mixture, the probe or the binding agent comprises a solution, and the solution is carried by surface tension by a tip of a pin and spotted on a plurality of positions on the biochip or the plate.